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心房颤动患者左心耳血栓相关研究进展

宋雪莉，张　娟*

山东大学第二医院心血管内科，山东　济南

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摘　要

心房颤动是一种快速、不规则的房性心律，与多种严重并发症相关的多系统疾病，卒中作为其并发症之一，是目前卫生系统面临的重大挑战。左心耳由于其独特的结构与功能，具有较大的个体差异性，成为非瓣膜性房颤患者血栓形成主要部位。近年来随着左心耳检查技术的发展，对于规律使用抗凝药物仍发生血栓事件患者，左心耳封堵术是一种新方向，所以研究左心耳结构与功能对血栓防治具有重要意义。

关键词

心房颤动，左心耳，血栓，左心耳封堵术

Research Progress on Left Atrial Appendage Thrombosis in Patients with Atrial Fibrillation

Xueli Song, Juan Zhang*

Department of Cardiology, The Second Hospital of Shandong University, Jinan Shandong

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Abstract

Atrial fibrillation (AF) is a multi-system disease with rapid and irregular atrial rhythm, which is associated with a variety of serious complications. Stroke, as one of its complications, is a major challenge to the health system at present. Due to left atrial appendage (LAA) unique structure and function, it has great individual differences, which has become the main site of thrombosis in patients with non-valvular AF. In recent years, with the development of LAA examination technology,

*通讯作者。

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LAA closure is a new direction for patients with thrombotic events despite regular use of anticoagulant drugs. Therefore, it is of great significance to study the structure and function of LAA for the prevention and treatment of thrombosis.

Keywords

Atrial Fibrillation, Left Atrial Appendage, Thrombosis, Left Atrial Appendage Closure

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1. 引言

心房颤动(简称房颤)是最常见的持续性心律失常，全世界患病率约为 2%~4% [1]，根据《全球疾病负担》，估计房颤的流行率高达 3350 万人，在一些国家影响到 2.5%~3.5%的人口[2]。房颤患者左心房血流动力学异常，可以引起血栓形成、心肌梗死和心力衰竭等并发症[3]，导致死亡风险增加 1.5~1.9 倍，短暂性脑缺血发作、卒中风险可增加 2~5 倍[4]。目前临床上通常用 CHA2DS2‑VASC 评分评估非瓣膜性房颤患者卒中风险，Jagadish P.S.等人[5]的研究表明，CHA2DS2-VASc 评分并没有纳入许多生理性房颤因素，表明 CHA2DS2-VASc 评分评估血栓风险有一定局限性。非瓣膜性房颤发生脑卒中患者栓子约 90%以上来源于左心耳[6]，因为左心耳独特的解剖结构、功能具有较大的个体差异性，其对血栓形成的作用不可忽视。左心耳封堵术是指采用介入方式，将封堵器经股静脉送至左心耳展开封堵，用于预防房颤脑卒中的手术治疗方法，因为其创伤小、恢复快等优点，近年来得到迅速发展[7]。本文综述了左心耳解剖结构、血流动力学对房颤患者形成血栓的影响，以及目前左心耳血栓的防治进展。

2. 左心耳形态与血流动力学

2.1. 左心耳解剖结构

左心耳是一个复杂的结构，在妊娠第 3 周发育，起源于主心房管的左侧和上级[8]，其明显小于其右侧的对应结构，并且小梁化严重，纤维平行排列[9]。左心耳是一个钩状结构，70%的时间形状是弯曲的[10]，其入口狭长，为血栓形成提供了理想的条件[11]。左心耳体部最常向前上方突出，与右心室流出道/肺动脉干的左侧边界和左主干或左回旋动脉重叠[12]，左心耳的长度平均为 45 mm，范围为 27~60 mm [13]，其内表面有梳状肌，并且相邻的梳状肌之间连接不太明显，使得左心耳表面变得不光滑，可能是容易造成血栓的原因[14]。左心耳突出部分称为分叶，在 500 例尸检病例的样本中，80%以上的左心耳是多分叶的(两个或两个以上的分叶)，这些分叶通常不位于同一平面上，使血流更容易淤积在左心耳，造成血栓形成[15]。现代成像技术已经能够对体内形态进行详细分析，左心耳形态主要被描述为“鸡翅型”，“风向袋型”、“菜花型”和“仙人掌型”，后三者统称为“非鸡翅型”。“鸡翅型”是最常见的形态，发生率为 48%，它有一个近端或中部弯曲的中央叶，可能有次级叶；“仙人掌型”是第二常见的类型(30%)，它有一个主要的中央叶和从主体向不同方向延伸的次级叶；“风向袋型”(19%)有一个长的主叶，可能有次级叶从它产生；“菜花型”(3%)最不常见，通常结构复杂，具有不同数量的次级叶[16]。Di Biase 等人[17]、Lupercio 等人[18]的荟萃分析也证实，与非鸡翅型房颤患者相比，鸡翅型左心耳房颤患者发生血栓栓塞的风险较低，可能因为“鸡翅型”左心耳容积更小，流速更快，结构相对简单，血流不容易发生淤

积，血栓发生率较低[19]。Kimura 等人[20]等人的一项研究表明，菜花型形态预测房颤患者心源性卒中(n = 30, OR = 3.355, p = 0.017)风险较高，可能因为菜花型具有更多的次级叶，小梁结构丰富，为血栓形成提供了有利的形态。

在 CT 成像中，左心耳开口有四种不同的形状，分别为圆形(5.7%)，水滴形(7.7%)，三角形(7.7%)和椭圆形(68.9%) [21]，并且 Elkind M.S.V.等人[22]发现较大的左心耳开口面积、长度和宽度与心源性卒中相关，最有可能是通过较大左心耳开口促进血栓排出的机制。Miki Y.等人[23]利用经食道超声心动图(TEE)测量左心耳开口面积发现其随着房颤时间的延长而逐渐增大，较大的左心耳开口面积有利于房颤患者血栓栓塞事件发生。另外 Beinart R.等人[24]发现左心耳深度较大的非瓣膜性房颤患者更容易发生脑卒中，可能因为血流容易在左心耳内产生涡旋，难以流出，促进血栓形成[25]。Jeong W.K.等人[26]研究表明左心耳体积和开口直径是房颤发生脑卒中的危险因子，同时也发现左心耳排空速度降低是非瓣膜性房颤血栓栓塞风险的标志物，大量研究表明“鸡翅型”左心耳具有最高的左心耳排空速度，中风和短暂性脑缺血发作的风险最低[17] [27]，并且 Wang F.等人[28]发现左心耳分叶增多与其流速降低有关，同时也是非瓣膜房颤患者发生血栓栓塞事件的危险因子，可能是因为左心耳直径越大，开口面积越大，流速越低，心房颤动时左心耳内的血流容易倒灌入左心耳内，促进血栓形成。

2.2. 左心耳血流动力学

左心耳除了其独特的解剖结构，功能异常也可能会增加心脏栓塞事件的易感性，当房颤患者左心耳功能失调时，收缩能力降低，血流速度减慢，随着房颤进展，左心房纤维化逐渐加重，导致左心耳开口扩张，从而促进血栓形成。左心耳是一个复杂而强大的器官，在窦性心律时，有其自主的收缩功能，使其能够调节左房压力并保证左室充盈。它是 30%的心房利钠肽因子池，在利钠作用中起重要作用，全身容量状态、运动和心房牵张的变化调节 ANP 分泌，促进全身液盐平衡[18]。Lee J.M.等人[19]发现左心耳可能与 RAAS 系统调节，潜在的触发/再进入有关，通过其收缩特性和神经激素肽的分泌来促进心脏血流动力学的变化和体积的平衡[20]。Waldemar 等人[29]证明左心耳功能降低与血栓形成有关，左心耳整体排空分数主要通过左心耳开口面积变化测量的，是公认的反映左心耳功能的指标[30]，Li J.等人[6]也证实左心耳整体排空分数可预测非瓣膜性房颤患者的血栓栓塞事件并改善卒中预测能力。

3. 左心耳检查方法

目前评估左心耳形态结构的成像方案包括经食管超声心动图(TEE)、心腔内超声心动图(ICE)、心脏磁共振(CMR)和计算机断层造影增强(CTCE) [31]。TEE 是目前房颤患者临床诊断左心耳血栓的金标准，是一种实时、快速、方便诊断左心耳血栓的方式，但是需要将探头置入食道，可能会导致食道穿孔、出血等创伤，口腔内容物误吸入气管，可能会发生吸入性肺炎，甚至窒息[32]。CMR 价格昂贵，花费时间较长，一般不用于排除左心耳血栓；ICE 能够全程、清晰的展现心腔内精细解剖结构，常应用于心律失常或结构性心脏病的介入手术，同时实时监测血流动力学变化，第一时间发现并发症，提高手术安全性[33] [34]，另外对于术前筛查心腔内血栓，多种研究表明其临床价值不逊于 TEE [35] [36]。值得注意的是，ICE 探头置于冠状静脉窦时，能够清晰的展示左心耳的截面图，但是由于 ICE 导管较硬，可能会有静脉穿孔或夹层的风险，虽然 ICE 价格较贵，但是对于由于情绪紧张、食管病变或其他原因不能行 TEE 或经 CTCE 检查不能排除左心耳血栓的患者，ICE 可以作为一种新选择[37]。目前 CT 增强扫描技术在临床上得到广泛应用，可以从不同角度和平面对心脏进行三维重组，显示其精细结构，并且可以更好的显示左心耳与心内或胸腔其他结构的解剖关系，具有高分辨率、无创、方便等优点；并且通过延迟显像，可以提高其准确性[38]。研究显示[39]在房颤的进展过程中，左心耳结构不断发生变化，导致 CT 表现不同。

由于成像原理不同，增强 CT 可能比 TEE 更早发现左心耳血流动力学紊乱，增强 CT + TEE 的联合应用可以更准确地评价 AF 患者的左心耳血流动力学，为准确的临床决策提供参考。

4. 左心耳血栓的防治

4.1. 药物治疗

CHA2DS2-VASc 评分是目前临床上应用最广泛的卒中风险评估工具，目前认为非瓣膜性房颤患者中女性≥3 分，男性≥2 分推荐口服抗凝药物；女性≥2 分，男性≥1 分可考虑抗凝治疗；而女性≤1 分，男性 0 分不推荐抗凝治疗[40]。值得注意的是，当患者为瓣膜性房颤或机械性心脏瓣膜置换时，无论 CHA2DS2-VASc 评分如何，除有抗凝禁忌外，患者都需要接受抗凝药物治疗。与此同时常用 HAS-BLED 评分评估出血风险，对于出血风险高患者，不应该停用抗凝药物，而应该对患者进行定期检查，评估指导药物使用，处理相关出血风险[41]。

经荟萃分析证实，非瓣膜性房颤患者长期口服维生素 K 拮抗剂(华法林)可以显著降低脑卒中等并发症的发生率[42]，但是由于起效缓慢(可同时予肝素，INR 达到目标范围停用肝素)，与多种食物及药物相互作用，具有狭窄的治疗窗(INR 比值大多维持在 2.0~3.0，根据不同年龄及机械瓣膜位置调节 INR)，常规检测 INR 及剂量调整较繁琐，其应用受到广泛限制。

目前新型口服抗凝药(NOAC)主要是通过特异性阻断凝血途径，治疗窗宽、效应剂量变化小，无需常规抗凝监测，可达到稳定的抗凝效果，在临床上广泛应用。多种研究表明，在非瓣膜性房颤中 NOAC 预防卒中和栓塞的发生风险不低于华法林，个别 NOAC 药物在降低颅脑出血风险基础上由于华法林，但 NOAC 药物发生胃肠道出血风险可能增高[43] [44]，但 NOAC 药物发生胃肠道出血风险可能增高。因其肾脏清除率不同，肾功能损害程度决定了选择合适的口服抗凝药物。值得注意的是，对于瓣膜性房颤或人工瓣膜置换术后患者，尚无证据证明可选用 NOAC，应选用华法林抗凝[45]。但目前我们面临着房颤患者抗凝率较低的问题，所以平时在医疗工作中加强对房颤患者的宣教，以及对医疗工作的综合评估和管理至关重要。

4.2. 外科手术治疗

长期口服抗凝药物是防止血栓形成的主要手段，然而受到患者依从性、长期治疗副作用及药物相互作用多种因素，传统的药物治疗并不是总能带来满意效果，有部分患者因担心出血风险高未规律服用抗凝药物，也有部分患者规律服用抗凝药物仍有血栓栓塞事件发生[46]。外科手术治疗主要包括左心耳内口闭合，左心耳结扎以及左心耳闭合，但是外科手术干预风险及创伤较大，且一般合并在其他心脏外科手术中进行，应用患者相对较少。

4.3. 左心耳封堵术

左心耳封堵术(LAAC)已发展成为房颤患者预防卒中的口服抗凝替代方案。目前，该手术推荐用于房颤、卒中风险升高和长期抗凝治疗禁忌症患者(IIb 类，证据等级 B) [47] [48]。LAAC 是使用器械封堵左心耳开口来防止血栓脱落进入血液，对左心耳形态结构及其周边组织评估很大程度上决定了手术是否成功，其属于微创介入治疗，相比于左心耳结扎术，具有创伤小、较安全的特性，2002 年，Sievert 等人[49]研究结果首次说明了植入封堵器的安全性、有效性；2009 年，Holmes 等人[50]通过多中心随机对照研究(PROTECT-AF)证实 LAAC 预防脑卒中风险疗效不低于华法林。Reddy 等人[51]研究也证实了 LAAC 的可行性、安全性及有效性。目前左心耳封堵装置主要包括 Watchman、Amulate、LAmbre、MemoLefort 等[52]，尚无证据表明封堵器之间有优劣程度之分。PRAGUE-17 多中心、随机研究证实在主要有效终点方面，

LAAC 与 NOAC 相比达到非劣效性。并且 Zhao M 等人[53]证实尽管患者有较高的 CHA2DS2-VASc 和 HAS-BLED 评分，但与 LAAC 后无卒中史的患者相比，既往卒中患者的临床预后并不差，LAAC 在降低既往有卒中的房颤患者血栓栓塞和心血管死亡风险方面的获益可能增加。LAAC 术后患者也可能会产生器械相关性血栓，预防血栓形成长期服用阿司匹林是常见的治疗策略，最近 Della Rocca DG 等人[54]、Zhou XD 等人[55]发现半剂量 DOAC 策略(半剂量 NOAC 加阿司匹林，此后长期半剂量 NOAC 单药治疗)显著降低了血栓形成事件和大出血事件复合终点的风险。目前国内相关临床经验较少，还需要进一步随机对照实验来确定 LAAC 术后最佳抗栓治疗策略。

5. 小结和展望

房颤是快速、不规则的房性心律，可以引起痴呆、卒中、心力衰竭等并发症，缺血性脑卒中是主要危害之一。血液高凝状态、血管壁异常和血流动力学变化，称为 Virchow 三联征，与此同时，血小板活性增加及凝血级联活化，导致血液高凝状态，以及心房压力逐渐升高，心房扩大，内皮细胞缺氧甚至坏死，加重炎症反应，促进一系列凝血机制发生。随着房颤进展，左心耳逐渐增宽和耳壁的不规则向内运动使得左心耳难以排空，容易淤血形成血栓。目前临床上多应用 TEE 或 CTCE 检查左心耳形态结构及有无血栓形成，两者联用可能更好的评估左心耳血流动力学，为临床决策提供更好的参考。目前抗栓方案，主要有药物治疗及手术治疗，药物治疗主要包含传统药物维生素 K 拮抗剂(华法林)及 NOAC，其各有优缺点，对于出血风险较高或口服抗凝药物情况下仍有血栓栓塞发生的房颤患者，可推荐应用左心耳封堵术，评估左心耳具体形态结构及其周围组织关系很大程度上决定了手术的成功。由于个体差异性，术后抗栓方案需要个体化定制，另外临床约 10%左右血栓非左心耳来源，所以我们要提高对房颤患者血栓形成相关因素的认识，优化卒中风险分层，对高危人群干预治疗，降低心源性卒中的发生。

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